Corticoid Therapy for Overlapping Syndromes in an HIV-positive Patient

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Abstract

Human immunodeficiency virus (HIV) infection disturbs the host’s immune function and often coexists with various autoimmune and/or systemic rheumatic diseases with manifestations that sometimes overlap with each other. We herein present the case of a 43-year-old Japanese man infected with HIV who exhibited elevated serum creatine kinase and transaminases levels without any symptoms. He was diagnosed with autoimmune hepatitis, polymyositis and Sjögren’s syndrome and received combined antiretroviral therapy (cART); however, the laboratory abnormalities persisted. We successfully administered cART with the addition of oral prednisolone, and the patient’s condition recovered without side effects related to the metabolic or immunosuppressive effects of these drugs.

Key words: human immunodeficiency virus (HIV), polymyositis (PM), Sjögren’s syndrome (SS), autoimmune hepatitis (AIH), steroid, combined antiretroviral therapy (cART)

Introduction

Human immunodeficiency virus (HIV)-infected patients sometimes present with a variety of autoimmune manifestations generated by the polyclonal stimulation of B cells and development of hypergammaglobulinemia (1). It has been reported that 4-71% of HIV-positive patients complain of rheumatic symptoms (2). HIV-infected individuals may develop multiple forms of autoimmune dysfunction, including vasculitis, rheumatologic conditions, HIV-associated connective tissue diseases and musculoskeletal disorders, such as arthritis/arthralgia or myalgia. Comorbid diseases include rheumatoid arthritis (RA), dermatomyositis (DM)/polymyositis (PM), systemic lupus erythematosus (SLE) and Sjögren’s syndrome (SS).

In addition, systemic rheumatic diseases are known to coincide with each other and/or autoimmune disorders, including autoimmune adrenal insufficiency (Addison’s disease), autoimmune hepatitis (AIH), autoimmune thyroid disease, antiphospholipid syndrome, biliary inflammatory diseases such as primary sclerosing cholangitis and primary biliary cirrhosis, celiac disease, inflammatory bowel diseases such as ulcerative colitis and Crohn’s disease, myasthenia gravis, sarcoidosis, type 1 diabetes mellitus and vasculitis (3).

Furthermore, HIV infection is often associated with various laboratory abnormalities, including the presence of antinuclear antibodies (ANA), antiplatelet antibodies, antilymphocyte antibodies, antigranulocyte antibodies or antiphospholipid antibodies and positive tests for direct antiglobulin (Coombs test), circulating immune complexes, rheumatoid factor or cryoglobulin. These autoimmune manifestations are generated by the polyclonal stimulation of B cells and development of hypergammaglobulinemia (1), as well as a state of predominant CD8 T cells and/or immune reconstitution due to effective treatment with combined antiretroviral therapy (cART) (4). However, it is very rare for HIV infection to coexist with two or more rheumatic and/or autoimmune conditions.
Moreover, approximately 21-32% of HIV-positive patients exhibit abnormal liver test results, mostly due to non-alcoholic fatty liver disease, followed by excessive alcohol use, chronic hepatitis B, chronic active hepatitis C and antiretroviral-induced hepatotoxicity (5, 6), whereas AIH is rarely observed in affected individuals.

We herein describe the case of an HIV-infected patient who developed AIH, SS and PM six years after contracting HIV. Managing autoimmune diseases with high doses of corticosteroids is usually very risky in HIV-infected patients; however, we were able to safely treat the present patient with corticosteroids under effective cART. In this report, we also review the pertinent literature and describe the clinical characteristics of patients with this disease presentation.

Case Report

The patient was a 43-year-old Japanese man who presented with lower limb weakness lasting for several months six years after receiving a diagnosis of HIV-1. He had a high serum creatine kinase (CK) level (313 IU/L; normal range: 800 to 1,500 IU/L). The patient also exhibited weakness during hip flexion (manual muscle testing; MMT=4/5) with no muscle wasting, hypertrophy or fasciculation. His power, reflexes, sensation and coordination were otherwise normal in both the arms and legs, as were the findings of gait and cranial nerve assessments and a general examination.

Laboratory tests revealed slightly high transaminases levels, with an AST level of 67 IU/L and ALT level of 59 IU/L. However, the γ-glutamyl transpeptidase (γ-GTP) (24 IU/L; normal range: 11-47) and alkaline phosphatase (ALP) (119 U/L; normal range: 115-359) levels were within the normal ranges. Furthermore, there were no abnormalities on renal or thyroid function tests, and the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level were both normal, although the CK level was high at 928 IU/L. Serological testing for hepatitis B and hepatitis C was negative.

Immunological tests demonstrated positive ANA, at a titer of 1/160; anti-SSA/Ro antibodies and anti-La/SSB antibodies were also positive. Accompanying hypergammaglobulinemia was also noted, with an elevated IgG level of 3,212 for long periods and a blood test revealed a CK level above 800 IU/L. He also gradually noted dry eyes and mouth. Four years later, he began treatment with abacavir/lamivudine (ABC/3TC) and ritonavir-boosted darunavir (DRV/r) containing cART due to a high viral load (13,000 copies/mL), low CD4 count (638 μL) and high serum CK level (1,360 IU/L). At the time, it was thought that the HIV infection may have caused the patient’s muscle disorder. One month later, the ABC/3TC therapy was switched to tenofovir/entecitabine (TDF/FTC) after he developed a skin rash.

Over two years after the initiation of the above regimen, the patient’s HIV viral load decreased to an undetectable level and his CD4 count increased to approximately 900 μL; however, his symptoms and transaminase levels did not improve, and the serum CK level remained high, ranging from 800 to 1,500 IU/L. The patient also exhibited weakness during hip flexion (manual muscle testing; MMT=4/5) with no muscle wasting, hypertrophy or fasciculation. His power, reflexes, sensation and coordination were otherwise normal in both the arms and legs, as were the findings of gait and cranial nerve assessments and a general examination.
fore diagnosed with polymyositis based on his clinical findings, without skin symptoms.

On admission, the patient was treated with oral steroids at an initial dose of 50 mg of prednisolone daily (1 mg/kg/day). His liver biochemistry improved, with a decrease in the AST level from 58 to 23 IU/L and a slight decline in the ALT level from 225 to 8 IU/L (normal range: 900-1,900) and IgM level of 419 mg/dL (34-190), although the IgA level was normal. No anti-JO-1 antibodies, anti-mitochondrial antibodies and anti-aminoacyl-tRNA synthetase (ARS) antibodies were detected.

Liver ultrasound demonstrated no abnormalities in the liver or biliary system, with no evidence of gallstones or biliary dilatation.

A liver biopsy showed active lymphoplasmacytic infiltration in some of the portal tracts, extending into the lobules, with spots of necroinflammatory changes also scattered within these regions (Fig. 1). These findings meet the diagnostic criteria for autoimmune hepatitis (positive autoimmune antibodies, high immunoglobulin levels, continuously high transaminase levels and negative serological tests for hepatitis B/hepatitis C).

Skeletal muscle magnetic resonance imaging (MRI) of the lower extremities also disclosed intramuscular inflammation as regions with an increased T2-weighted signal (Fig. 2). Furthermore, a muscle biopsy with subsequent histochemical staining demonstrated many necrotic and regenerating muscle fibers surrounded and infiltrated by mononuclear cells, including lymphocytes (Fig. 3A, B). The patient was therefore diagnosed with polymyositis based on his clinical (proximal muscle weakness, an increased serum CK level of 928 U/L and increased ESR of 44 mm/1 h) and pathological findings, without skin symptoms.

Maraviroc was added to the cART regimen for six months; however, the patient’s symptoms did not improve. It subsequently became difficult for him to climb two stairs per stride. A physical examination was normal, with the exception of slight proximal muscle weakness in the lower limbs, primarily in the hip flexors. Further investigations revealed an apple tree appearance on sialography (Rubin-Holt classification, stage 1, Fig. 4). In addition, histopathology of a salivary gland biopsy showed focal lymphoplasmacytic infiltration and fibrosis around the salivary ducts (Fig. 5A, B), and Schirmer’s test was positive in the right eye (9 mm/10 min in the right eye and 12 mm/10 min in the left eye), although the gam test was negative (12 mL/10 min). These findings met 3/4 of the diagnostic criteria for SS (sialographical findings, histopathological features and positive autoantibodies).

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Figure 4. On sialography, there is a normal central ductal system, but it is slightly tortuous (arrow), and numerous peripheral punctate collections of contrast material (1 mm or less in diameter) are scattered uniformly throughout the gland (“an apple tree appearance”) (circles). These findings are classified as stage 1 using the Rubin-Holt classification.

Figure 5. A, B: A salivary duct is surrounded by lymphocytes with plasma cells (arrows), and the salivary gland parenchyma has been replaced by some parts of fibrotic fibers (arrowheads). However, there are no inflammatory cells filling the lumen of the salivary ductile, which is a normal shape. C: Histoimmunochemistry analyses of salivary gland tissue reveal aggregates of inflammatory cells including few CD4⁺ T lymphocytes around the salivary ductile (arrowheads). D: CD8⁺ T lymphocytes infiltration of the surrounding salivary gland tissue was also observed (arrowheads). Interestingly, there is invading of several CD8⁺ T lymphocytes through the basement membrane of salivary ducts (arrows), and yet basal cell layer and basement membrane are intact.

ALT level from 42 to 30 μmol/L after only two weeks of prednisolone therapy. The serum CK level also decreased from 963 to 94 IU/L, although slight muscle weakness persisted.
The dose of prednisolone was gradually reduced to under 15 mg a day, without adverse events, such as opportunistic infections or the activation of dormant infections. Furthermore, the patient’s symptoms did not relapse, and the CK and transaminases levels have remained in the normal range (Fig. 6).

**Discussion**

**AIH coincides with HIV infection**

There are many causes of hepatitis in HIV-positive patients, including HIV itself, complicated hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, adverse drug events, opportunistic infections and metabolic or autoimmune disorders. In the present case, the patient’s liver dysfunction improved following treatment with corticosteroid therapy, but not cART. In addition, serological testing for hepatitis B and hepatitis C was negative. Therefore, we concluded that he had AIH.

Although the etiology of AIH is not entirely clear, the disease appears to be associated with autoimmune antibodies. Approximately 1,400 new patients with this condition are diagnosed each year in the general population in Japan, with a female: male ratio of 6:1. However, only seven cases of AIH in patients with HIV have been reported in the medical literature (7). In one case, a patient was diagnosed with HIV and HCV. In that report, Pietro et al. (8) described cross-reaction between anti-liver kidney microsome (LKM)-1 antibodies against CYP2D6 (presenting in a patient with AIH type 2) and HCV, herpes simplex virus (HSV) and cytomegalovirus (CMV). The authors concluded that liver damage in AIH type 2 patients is caused by both CYP2D6-specific CD4 T cells and human leukocyte antigen (HLA) class I-restricted CD8 T cells.

In the present report, the histological findings of the liver biopsy showed interface hepatitis with predominantly lymphoplasmacytic nercroinflammatory infiltrates, without portal-portal or central-portal bridging necrosis, liver cell rosette formation, nodular regeneration, bile duct damage or the presence of well-defined granulomas. These positive and negative findings meet the diagnostic criteria for AIH proposed by the International Autoimmune Hepatitis Group (9).

In some cases, HIV infection is considered to be the causative agent, whereas other patients present with diffuse infiltrative lymphocytosis syndrome (DILS). Among non-HIV infected patients, roughly 33-80% have an autoimmune or systemic rheumatic disease, including SS (7.2-8.4%), RA (2.8-4.2%) or SLE (2.6-2.8%) (10, 11).

According to Puius et al. (7), there is only one reported case in which the patient’s condition improved with cART and three cases in which standard AIH therapy was successful. Therefore, the proper therapy must be selected on a case-by-case basis, targeting the specific causes underlying the patient’s condition.

**PM coincides with HIV infection**

Myalgia itself is not rare in HIV-positive patients. The incidence of myalgia in patients infected with HIV has been reported to be as high as 77% (12-15).

Muscular disorders associated with HIV in adults include rhabdomyolysis, zidovudine (AZT) myopathy, HIV-associated DM/PM, inclusion body myositis, nemaline rod
myopathy, wasting syndrome and pyomyositis (4, 12).

Masanés et al. (16) classified myopathies associated with HIV into four categories: i) myopathy caused by opportunistic microorganisms; ii) inflammatory and/or necrotizing myopathy or vasculopathy; iii) myopathy of unclear etiology (i.e., nemaline myopathy and loss of thick filaments); and iv) myopathy with histological minimal or unspecific changes, such as type 2 fiber atrophy.

HIV-associated PM has been described in up to 2-7% of patients, with one-third of cases involving an inflammatory condition on a skeletal muscle biopsy (4, 17). Although HIV-associated PM is rarely associated with HIV CD4 T cells, the muscle is typically infiltrated with CD8 T cells. In the present case, immunohistochemistry showed various types of inflammatory cells accumulated around necrotic muscle tissue. These cells predominantly included CD8+ T lymphocytes and CD4+ T lymphocytes (Fig. 3C, D). Immunohistochemical analyses of the muscle tissue in cases of HIV-associated PM tend to show a significant decrease in endomyosal CD4+ T lymphocytes, although these findings cannot be used to distinguish the condition from cases of non-HIV PM (17). Therefore, the muscle infiltrates observed in patients with SS consist of a mixture of B and T cells, with the proportions of CD4+ and CD8+ lymphocytes varying based on the individual case (18). In this manner, the molecular mechanisms underlying the development of myositis associated with SS and/or PM may have contributed to the onset of inflammatory myopathy noted in the present patient.

The detection of viral antigens and nucleic acids in endomyosal lymphocytes and deposition of complement and immune complexes in the endomysial capillary wall may be triggered by molecular mimicry (4, 19). Therefore, myopathies accompanied by DILS are often indistinguishable from those of PM (4). The pathogenesis of PM in the context of HIV infection is more responsive to immunosuppressive or corticoid therapy and may even resolve spontaneously (4, 16). However, it remains controversial whether cART is effective in HIV-positive patients with PM (20). In the present case, cART had no effect on the patient’s myositis, whereas corticosteroids were markedly effective. This finding reveals that this particular case of myositis was likely caused by an immune response.

**SS coincides with HIV infection**

The overall prevalence of DILS in the HIV-1-positive population is 1.5-3% (21), and we have previously demonstrated that tear production is significantly decreased in 42.9% of HIV-infected patients (22). DILS, similar to Sjögren’s-like and HIV-associated sicca syndromes, has the following features: bilateral parotid and lacrimal glandular swelling, xerostomia and keratoconjunctivitis of varying intensity frequently accompanied by persistent CD8 peripheral lymphocytosis and visceral infiltration with CD8+ T cells (22, 23). On the other hand, SS is histologically characterized by exocrine glands infiltrated predominantly by CD4+ T lymphocytes (17, 24). The present patient’s immunohistochemical results revealed diffusely infiltrating cells consisting predominantly of CD8+ T lymphocytes around a salivary duct and in the ductal epithelium, with CD4+ T lymphocytes being less prominent (Fig. 5C, D). One reason for this phenomenon may be that, as more inflammatory cells infiltrate around salivary glands in patients with Sjögren’s syndrome, the CD4+/CD8+ T lymphocyte ratio further decreases, while the infiltrating CD8+ T lymphocyte count remains unchanged (25). Furthermore, since the total CD4 count in the current patient was originally decreased due to HIV infection, there may have been little CD4 invasion in the lesion as compared with that observed in patients without HIV infection. However, the likelihood of complications of SS should not be denied. The laboratory findings of patients with HIV-associated sicca syndrome usually show negative autoantibodies, including SS-A and SS-B (22). HIV-associated sicca syndrome is primarily caused by DILS, likely due to chronic viral infection. However, in the present case, both SS-A and SS-B autoantibodies were positive. Therefore, the sicca syndrome noted in this case appears to be attributable to an autoimmune response.

Walker et al. (4) noted extraglandular complications of DILS consistent with lymphoid interstitial pneumonitis (31%) and muscular (26%) and hepatic (23%) involvement. They also reported that findings of negative autoantibodies and rheumatoid factor (RF), with positive HLA-DR5 and HLA-DRB1 results, are useful for distinguishing DILS from SS and suggested that the declining incidence of DILS in the cART era is due to the effects of antiretroviral therapy.

Some drugs induce salivary gland damage in addition to liver dysfunction, leading to the co-development of AIH and SS, although it is unclear whether a common pathology underlies these two conditions (26-28).

**HIV and autoimmune antibodies**

The proportion of RF-positive patients ranges between 3.2% and 10% among those with HIV, with significantly higher RF values than those observed in healthy controls (13, 29, 30). In addition, ANA are noted in 3-84% of affected individuals, while circulating immune complexes are detected in 82-98% of cases (4, 13, 29). In contrast, the C3 and C4 complement levels are normal in some cases, whereas antineutrophil cytoplasmic antibodies (ANCA) are detected at a high frequency (4).

Henriksson et al. (31) reported that serum IgG antibodies against CD4 T cells are found in 12.6% of patients with primary SS and 13.0% of individuals positive for HIV. The generation of autoantibodies in patients suffering from HIV infection suggests polyclonal B cell function hyperactivity (18). In fact, light chain restriction without IgH rearrangement has been detected in reactive lymph nodes in patients with Castleman’s disease, as well as autoimmune and viral disorders, such as herpes virus 6, Epstein-Barr virus (EBV) and HIV (32). The mechanism underlying the formation of circulating antibodies to HIV p24 proteins in SLE
and SS patients without HIV infection may resemble that of cross-activity between U1 snRNP 70 antibodies and HIV pol proteins noted in systemic sclerosis patients (17).

Immune reconstitution syndrome also causes autoimmunity in HIV-positive patients. The development of autoimmune diseases of the thyroid gland, such as Grave’s disease, soon after the initiation of cART is not rare (33, 34). Reduced autoimmunity may manifest as immune reconstitution in patients treated with cART. In the present case, the CK level was not initially elevated, and there were no clear muscle symptoms prior to the initiation of cART. However, the CK level increased and the patient developed muscle weakness shortly after receiving cART. Immune reconstitution due to cART may worsen cases of mild PM.

Zhang et al. (14) clinically classified rheumatic manifestations in patients with HIV infection into four categories: (i) mimicry of rheumatic diseases; (ii) complication with rheumatic diseases; (iii) immunological abnormalities in cases of HIV infection; and (iv) immune reconstitution of inflammatory syndromes caused by cART therapy. It is difficult to distinguish between these categories, especially autoimmune dysfunction caused by HIV itself or the effects of antiretroviral therapy.

Capetti et al. (20) described the anti-inflammatory effects of an antiretroviral regimen containing maraviroc in an HIV-positive patient with secondary myositis. However, our patient continued to experience muscle weakness and his CK level remained above 500 IU/L after changing the cART therapy. Neither maraviroc nor cART were effective for autoimmune disease in this case; only corticosteroid therapy effectively treated the patient’s condition (Fig. 6).

The administration of immunosuppressive therapy, such as high-dose corticosteroid treatment, is usually risky in HIV-positive patients, although it may be relatively safe under effective cART. In the present case, the patient demonstrated a prompt recovery of muscle strength with normal laboratory test results following the administration of prednisolone as the standard therapy for AIH and PM.

The simultaneous development of AIH, SS and PM in an HIV patient is exceedingly rare. The immunological findings of this case provide useful information for understanding the pathogenesis of autoimmune diseases.

The authors state that they have no Conflict of Interest (COI).

References
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